

## ORIGINAL PAPER

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# Relationship of Nosocomial Infections with the Development of Necrotizing Enterocolitis in Preterm Infants

Zlatan Zvizdic<sup>1</sup>, Suada Heljic<sup>2</sup>, Alena Firdus<sup>1</sup>, Asmir Jonuzi<sup>1</sup>, Denisa Zvizdic<sup>3</sup>Clinic of Pediatric Surgery, Clinical Centre University of Sarajevo, Sarajevo, Bosnia and Herzegovina<sup>1</sup>Pediatric Clinic, Neonatal Intensive Care Unit, Clinical Center University of Sarajevo, Sarajevo, Bosnia and Herzegovina<sup>3</sup>Eye Clinic, Clinical Centre University of Sarajevo, Sarajevo, Bosnia and Herzegovina<sup>3</sup>

Corresponding author: Zlatan Zvizdic, MD, PhD, Clinic of Pediatric Surgery, Clinical Center University of Sarajevo, Sarajevo, Bosnia and Herzegovina. Phone: +387 33 297 142; Email: zlatan.zvizdic@gmail.com

## ABSTRACT

**Objective:** The aim of this study was to determine the association between the number of nosocomial infections prior to necrotizing enterocolitis (NEC) diagnosis as well as to evaluate how it contributed to development of NEC in premature infants. **Material and Methods:** The study included 51 preterm infants diagnosed with NEC and 71 preterm infants without NEC hospitalized in the neonatal intensive care unit (NICU) of Clinical Center University of Sarajevo. We evaluated the correlation of the number of nosocomial infections prior to NEC diagnosis with the development of NEC. **Results:** There was a statistically significant association of the number of nosocomial infections prior to NEC diagnosis with the development of NEC (odds ratio, 3.32; 95% confidence interval, 1.09-10.01). **Conclusion:** Increased number of nosocomial infections prior to NEC diagnosis is associated with increased risk of necrotizing enterocolitis.

**Key words:** Nosocomial infections, Necrotizing enterocolitis, Preterm infants.

## 1. INTRODUCTION

Necrotizing enterocolitis (NEC) is an acquired inflammatory disease of the gastrointestinal tract (GIT) characterized by coagulation necrosis and inflammation of the intestine in a neonate (1). The incidence of NEC is 0.5-3.5 per 1000 live births (2, 3). NEC affects mostly preterm infants (2). NEC in term infants is usually associated with conditions such as congenital anomalies, sepsis, or hypotension (4). It has documented that the incidence of NEC increases with decreasing birth weight (BW) and gestational age (GA) (3). The age of onset is highly variable and inversely correlated with GA (3). The mortality rate associated with NEC ranges between 20 to 30%, with the highest rate in infants who had undergone surgery (5). Approximately 27-63% of affected infants require surgery (6). Prematurity (with immature GIT and host defenses) is the primary risk factor (7). In addition, various studies have identified other risk factors for the development of NEC (8, 9); however, the definite aetiology still eludes modern medical research.

In this study, we retrospectively determined the association between the number of nosocomial infections prior to NEC diagnosis as well as evaluated how it contributed to development of NEC in preterm infants admitted in the NICU of Clinical Center University of Sarajevo.

## 2. PATIENTS AND METHODS

In accordance with the Helsinki declaration, the Institutional Review Board (IRB), and the Independent Ethics Committee of Clinical Center University of Sarajevo (CCUS) approved all aspects of this study. This retrospective study was performed on all preterm infants (<37 weeks gestation at birth) admitted in the NICU of CCUS during a period of 5 years, from 2008 to 2012. Gestational age was determined by early ultrasound and recorded as completed weeks. This study examined the number of nosocomial infections prior to NEC diagnosis.

Nosocomial infection was defined and categorized in accordance with the NNIS/CDC, Atlanta criteria (10, 11). Definition of nosocomial infection (NI): NI infection is defined as an infection that occurs after 48 hours of hospitalization, resulting in a positive blood, cerebrospinal fluid (CSF), or urine culture with clinical manifestations such as hospital-acquired bloodstream infections, nosocomial pneumonia, sepsis, urinary tract infection and meningitis.

For the purposes of this analysis, a diagnosis of NEC was made based on the presence of clinical, radiological and/or histopathological evidence that fulfilled the criteria of Bell's (12) as well as Walsh's modification of these criteria (13). Definition of necrotizing enterocolitis:

|  |                                       |                              |
|--|---------------------------------------|------------------------------|
| Presence of TWO of following clinical signs and symptoms without any other recognised reasons: | AND ONE of the following criteria: OR |                              |
| VOMITING   | PNEUMOPERITONEUM                      | HISTOLOGICAL EVIDENCE OF NEC |
| ABDOMINAL DISTENSION   | PNEUMATOSIS INTESTINALIS              |                              |
| PRE-FEEDING RESIDUAL   | FIXED DILATED LOOP                    |                              |
| REDNESS OF FLANKS  |                                       |                              |
| MICROSCOPIC OR GROSS BLOOD IN STOOLS   |                                       |                              |

Table 1 Definition of NEC

Medical NEC was defined as the presence of radiological signs of pneumatosis intestinalis and when the disease is treated with antibiotics for more than two days. Surgical NEC was defined as any surgical treatment. Of all 830 premature infants, 51 preterm infants met the criteria for NEC in this analysis. The control group consisted of 71 randomly selected preterm infants that were not significantly different by BW and GA from premature infants with NEC.

A standardised format was used for data collection. The infants's medical records were reviewed daily for medical course informations until hospital discharge or death of infant.

### 3. STATISTIC ANALYSIS

Statistical analysis was performed using SPSS 16.0 (SPSS Inc, Chicago, IL, USA). The number of nosocomial infections was compared between infants with and without NEC. Categorical variables were compared using the  $\chi^2$  test. The means of continuous variables were compared using Student's t test, and the data are presented as mean (SD). The influence of relevant confounding variables, identified by univariate analysis, was assessed using multivariate logistic regression analysis. Confidence intervals presented for odds ratios are adjusted for the clustering of infants within participating nurseries (14). Statistical level of 95% ( $p < 0.05$ ) was considered as significant for all performed tests.

### 4. RESULTS

During the study period, 830 preterm infants were admitted in the NICU; 51 (6.1%) got NEC. In the group of patients with NEC, based on the diagnostic criteria (12, 13), established the existence of the medical NEC in 30 patients (58.8%) while the surgical NEC was found in 21 patients (41.2%).

The frequency of nosocomial infections prior NEC diagnosis is presented in Figure 1.

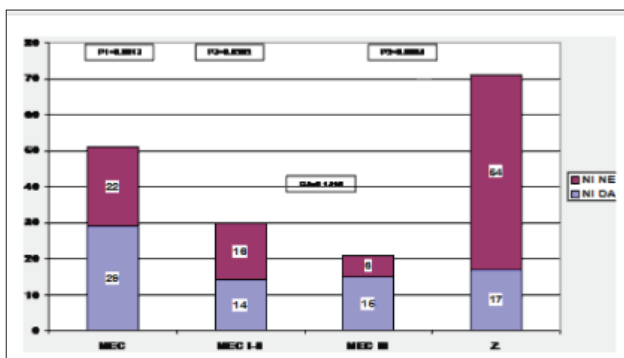


Figure 1. The frequency of nosocomial infections prior to NEC diagnosis.

There are presented the frequency of NI in the collective group of patients with NEC ( $n=51$ ), in medical NEC group (NEC I-II) ( $n=30$ ), in surgical NEC group (NEC III) ( $n=21$ ) and in the control group (Z) ( $n=71$ ),  $p < \text{probability}$

Results presented in Figure 1. showed that 56.9% (29/51) of premature infants with NEC had at least one or more of NI prior to NEC diagnosis. Further analysis showed that 46.7% (14/30) preterm infants with medical NEC and 71.4% (15/21) preterm infants with surgical NEC had at least one or more NI prior to diagnosis of NEC. In the control group of patients, NI's were present in 23.9% (17/71). Chi square test of independence (with Yates' correction for continuity) showed a significant correlation between the frequency of NI and the development of NEC in the collective group of patients with NEC compared to the control group. A statistically significant difference was observed between the NEC group of patients compared to the control group  $\chi^2$  (1,  $N = 122$ ) = 12.328,  $p = 0.0004$ , between the medical NEC group (NEC I-II) compared to the control group  $\chi^2$  (1,  $N = 101$ ) = 4.106,  $p = 0.0427$ , and between the surgical NEC group (NEC III) compared to the control group  $\chi^2$  (1,  $n = 92$ ) = 14.084,  $p=0.0002$ . This test showed no significant correlation between the frequency of NI in collective group of patients with NEC compared to patients with medical or surgical NEC.

Logistic regression analysis of six continuous variables (number of days of on mechanical ventilation, number of nosocomial infection, number of days of prescribed H2 blockers, morphine sulfate, inotropes, number of received red blood cell transfusions) prior to NEC diagnosis was deemed statistically significant.

Logistic regression analysis of risk factor (nosocomial infections) associated with the development of necrotizing enterocolitis is presented in Table 2.

| Factor                | P      | OR     | 95% CI for OR    |
|-----------------------|--------|--------|------------------|
| Nosocomial infections | 0,0333 | 3,3169 | 1,0993 – 10,0086 |

Table 2. Logistic regression analysis of risk factor (nosocomial infections) associated with the development of necrotizing enterocolitis.

Logistic regression analysis showed that there was a statistically significant association of the number of nosocomial infections prior NEC diagnosis with the development of NEC (odds ratio, 3.32; 95% confidence interval, 1.09-10.01). Based on the result of logistic regression analysis, it can be concluded that each additional infection increased the odds of developing NEC by 3 times. No relationship was identified between the number of nosocomial infections and gender.

### 5. DISCUSSION

Result of our study of 6.1% preterm infants with NEC among the total percentage of hospitalized preterm infants in the NICU of CCUS is in accordance with the results of studies that recorded the frequency of these patients in the total percentage of admission to the NICU from 1-7.7% (15).

Preterm infants are at increased risk of infectious diseases due to the immaturity of their immune system and prolonged

hospital stay (16). Nosocomial infections (NI) cause a huge burden of morbidity and mortality and include bloodstream, urine, cerebrospinal, peritoneal, and lung infections as well as infections starting from burns and wounds, or from any other usually sterile sites (17). Bloodstream infection is the most common nosocomial infection in the NICU setting (18). NI's are responsible for almost 50% of the infants mortality rate in the first two weeks of life (19).

Numerous studies that looked at association of the increased number of nosocomial infections with the development of NEC found that the increased number of nosocomial infections prior to NEC diagnosis correlated with an increase in the development of NEC (19). Extremely low BW infants with NEC were found to have more culture-proven sepsis than infants without NEC (20). It was also observed that preterm infants with predisposing clinical conditions, when exposed to an infectious agent, could experience intestinal ischemia leading to the development of NEC (21). Although it is not yet known the exact reason for the connection between of nosocomial infections with the development of NEC, it is assumed that the reason also might lie in the increased length of the utilization of total parenteral nutrition in these preterm infants, which has resulted in an immunosuppressive effect by reducing the degree of phagocytosis and consequent inability of neutralizing the coagulase-negative staphylococci (22).

Results of our study found that the number of nosocomial infections prior to NEC diagnosis in the group of patient with NEC was statistically significantly higher correlated to the control group ( $p = 0.0004$ ). Also the exposure of nosocomial infections was significantly higher in the medical NEC group ( $p = 0.0427$ ) as well as in the surgical NEC group ( $p = 0.0002$ ) correlated with the control group. In logistic regression analysis with six independent variables (nosocomial infections, mechanical ventilation, morphine sulfate, inotropes, red blood cell transfusion and H2-blocker therapy), applied to assess the influence of these multiple factors on probability of developing NEC, the number of nosocomial infection prior to NEC diagnosis has significantly contributed to the model, suggesting that the increased number of nosocomial infections in preterm infants increases probability of developing NEC three times. Our results are in accordance with the results of studies that found a significant effect of nosocomial infections on the development of NEC (16, 19, 22, 23).

Furthermore, the results of our research showed that preterm infants with lower GA and BW had a significantly higher number of nosocomial infections and more serious stage of NEC compared with premature infants born at later gestational ages and with higher BW. This difference may be due to the fact that infants who are of lower GA and BW being at higher risk for infection than infants weighing more than 1500 grams because of several factors associated with NICU admission such as poor handwashing techniques, central venous catheters, mechanical ventilation and poor skin cleansing prior to invasive techniques. Our results are in accordance with the results of other studies that have found that preterm infants with lower GA and BW have a higher sensitivity for the development of nosocomial infections and more serious stages of NEC (24, 25).

## 6. CONCLUSION

Preterm infants who developed NEC had significantly higher number of nosocomial infections prior to developing NEC than those who did not develop NEC. Identifying risk factors for NEC, through the findings that the number of nosocomial infections strongly correlated with the development of NEC, could lead to clinical applications of crucial infection control practices in the healthcare settings to minimize risk of NEC in preterm infants.

**CONFLICT OF INTEREST: NONE DECLARED.**

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